



PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1129WOORD01	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/4.16)	
International application No. PCT/EP 03/08676	International filing date (day/month/year) 06.08.2003	Priority date (day/month/year) 10.08.2002
International Patent Classification (IPC) or both national classification and IPC C07D401.04		
Applicant ALTANA PHARMA AG		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none">I <input checked="" type="checkbox"/> Basis of the opinionII <input type="checkbox"/> PriorityIII <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicabilityIV <input type="checkbox"/> Lack of unity of inventionV <input checked="" type="checkbox"/> Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statementVI <input type="checkbox"/> Certain documents citedVII <input type="checkbox"/> Certain defects in the international applicationVIII <input type="checkbox"/> Certain observations on the international application		
Date of submission of the demand 17.02.2004	Date of completion of this report 16.04.2004	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 apmu d Fax: +49 89 2399 - 4465	Authorized Officer Kyriakakou, G Telephone No. +49 89 2399-7835 	

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I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-29 as originally filed

Claims, Numbers

1-17 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
 - ☐ the language of publication of the international application (under Rule 48.3(b)).
 - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:
- ☐ contained in the international application in written form.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority in written form.
 - ☐ furnished subsequently to this Authority in computer readable form.
 - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
4. The amendments have resulted in the cancellation of:
- ☐ the description, pages:
 - ☐ the claims, Nos.:
 - ☐ the drawings, sheets:
5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 16 and 17 in respect of industrial applicability

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-17
	No: Claims	
Inventive step (IS)	Yes: Claims	1-17
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-15
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 16 and 17 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Cited Documents

1.1. Certain published documents (Rule 70.10)

WO-A-02085906 (=D1)

WO-A-02064584 (=D2)

1.2 Reference is made to the following Documents.

WO-A-0130777 (=D3)

WO-A-9931090 (=D4)

WO-A-9931071 (=D5)

WO-A-9831674 (=D6)

WO-A-9307146 (=D7)

J.Med. Chem. 2001,44,2523 (=D8)

J.Med. Chem. 2002,45,2520 (=D9)

J.Med. Chem. 2002,45,2526 (=D10)

The indicated designation is used throughout the examination procedure

3. Novelty

The present application and the prior art Documents D3-D10 relate to **2-N-substituted-pyridazinones**. The main structural difference resides in the nature of the "-N-substituent.

The subject matter of the present claims 1-17 can therefore be considered to be novel.

4. Inventive step

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4.1 The object of the present invention is to provide compounds useful as PDE4 inhibitorss.

4.2 In the light of the pharmacological tests comprised in the Description (28-29) it is considered as credible that a limited number of the claimed compounds have the alleged activity.

4.3 The prior art documents D3-D10 which disclose structurally similar pyridazinone derivatives having PDE4 inhibitory activity are considered to be especially relevant. With respect to the said prior art documents the main structural difference lies in the modification of the 2N--substituent of the pyridazinone. Taking the above into account it is evident for the person skilled in the art that the pyridazinone group is fundamental for the PDE4 inhibitory activity and further modification of the substituents results to more or less potent agents while the PDE4 inhibitory activity is maintained. The claimed compounds are therefore considered to be prima facie obvious and an inventive step cannot be acknowledged,

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/04 C07D405/14 A61K31/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 02 085906 A (ALTANA PHARMA AG) 31 October 2002 (2002-10-31) cited in the application page 31 -page 41; claims 1-13 ---	1-17
P,A	WO 02 064584 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) 22 August 2002 (2002-08-22) cited in the application page 25 -page 36; claims 1-13 ---	1-17
Y	WO 99 31090 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) 24 June 1999 (1999-06-24) cited in the application page 34 -page 38; claims 1-10 --- -/-	1-17



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

24 November 2003

Date of mailing of the international search report

12/12/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Kyriakakou, G

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01 30777 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) 3 May 2001 (2001-05-03) cited in the application page 21 -page 25; claims 1-10 ---	1-17
Y	WO 99 31071 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) 24 June 1999 (1999-06-24) cited in the application page 32 -page 36; claims 1-10 ---	1-17
Y	WO 98 31674 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) 23 July 1998 (1998-07-23) cited in the application page 49 -page 55; claims 1-10 ---	1-17
Y	WO 93 07146 A (SYNTEX INC.) 15 April 1993 (1993-04-15) cited in the application page 162 -page 169; claims 1-33 ---	1-17
Y	MARGARETHA VAN DER MEY ET AL.: "Novel Selective Phosphodiesterase (PDE4) inhibitors. 4. Resolution, Absolute Configuration and PDE4 Inhibitory Activity of cis-Tetra- and cis-Hexahydrophthalazinones" JOURNAL OF MEDICINAL CHEMISTRY., vol. 45, no. 12, 6 June 2002 (2002-06-06), pages 2526-2533, XP002262562 AMERICAN CHEMICAL SOCIETY., US ISSN: 0022-2623 cited in the application the whole document ---	1-17
Y	MARGARETHA VAN DER MEY ET AL.: "Novel Selective PDE4 Inhibitors.3. In Vivo Antiinflammatory Activity of a New Series of N-Substituted cis-Tetra- and cis-Hexahydrophthalazinones" JOURNAL OF MEDICINAL CHEMISTRY., vol. 45, no. 12, 6 June 2002 (2002-06-06), pages 2520-2525, XP002262563 AMERICAN CHEMICAL SOCIETY., US ISSN: 0022-2623 cited in the application the whole document --- -/--	1-17

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>MARGARETHA VAN DER MEY ET AL.: "Novel Selective PDE4 Inhibitors. 2. Synthesis and Structure-Activity Relationships of 4-Aryl-Substituted cis-Tetra- and Cis-Hexahydrophthalazinones" JOURNAL OF MEDICINAL CHEMISTRY., vol. 44, no. 16, 2 August 2001 (2001-08-02), pages 2523-2535, XP002222951 AMERICAN CHEMICAL SOCIETY., US ISSN: 0022-2623 cited in the application the whole document</p> <p>-----</p>	1-17

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 16 and 17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 02085906	A	31-10-2002	WO 02085906 A2	31-10-2002
WO 02064584	A	22-08-2002	CA 2438520 A1	22-08-2002
			EE 200300311 A	15-10-2003
			WO 02064584 A1	22-08-2002
			EP 1362044 A1	19-11-2003
WO 9931090	A	24-06-1999	AU 753576 B2	24-10-2002
			AU 2270199 A	05-07-1999
			CA 2314111 A1	24-06-1999
			EE 200000335 A	15-10-2001
			WO 9931090 A1	24-06-1999
			EP 1042319 A1	11-10-2000
			HU 0004561 A2	28-03-2002
			JP 2002508368 T	19-03-2002
			PL 341239 A1	26-03-2001
			US 6380196 B1	30-04-2002
WO 0130777	A	03-05-2001	AU 1515101 A	08-05-2001
			BR 0014990 A	18-06-2002
			CA 2388119 A1	03-05-2001
			CN 1382137 T	27-11-2002
			CZ 20021457 A3	17-07-2002
			WO 0130777 A1	03-05-2001
			EP 1244654 A1	02-10-2002
			HU 0203487 A2	28-02-2003
			JP 2003512466 T	02-04-2003
			NO 20021959 A	29-05-2002
			SK 7232002 A3	10-09-2002
			TR 200201128 T2	21-08-2002
			US 6544993 B1	08-04-2003
			US 2003166655 A1	04-09-2003
			ZA 200203157 A	10-04-2003
WO 9931071	A	24-06-1999	AU 1760399 A	05-07-1999
			WO 9931071 A1	24-06-1999
WO 9831674	A	23-07-1998	AT 233247 T	15-03-2003
			AU 735934 B2	19-07-2001
			AU 5862998 A	07-08-1998
			BR 9806752 A	14-03-2000
			CN 1127487 B	12-11-2003
			DE 69811645 D1	03-04-2003
			DK 971901 T3	10-06-2003
			EA 2764 B1	29-08-2002
			EE 9900274 A	15-02-2000
			WO 9831674 A1	23-07-1998
			EP 0971901 A1	19-01-2000
			HU 0001541 A2	28-05-2001
			IL 130659 A	25-07-2002
			JP 2001508078 T	19-06-2001
			NO 993301 A	10-09-1999
			NZ 336573 A	27-10-2000
			PL 334561 A1	13-03-2000
			PT 971901 T	31-07-2003
			SI 971901 T1	31-10-2003
			SK 95199 A3	10-12-1999
			TR 9901653 T2	21-10-1999

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9831674	A	US 6103718 A	15-08-2000
WO 9307146	A	15-04-1993	
		AT 183745 T	15-09-1999
		AU 670544 B2	25-07-1996
		AU 2781592 A	03-05-1993
		CA 2117059 A1	15-04-1993
		DE 69229874 D1	30-09-1999
		DE 69229874 T2	09-12-1999
		DK 612321 T3	13-12-1999
		EP 0612321 A1	31-08-1994
		ES 2105920 A1	16-10-1997
		ES 2135416 T3	01-11-1999
		FI 941567 A	06-04-1994
		GR 3030969 T3	30-11-1999
		HU 66969 A2	30-01-1995
		HU 9500113 A3	28-06-1995
		IL 103388 A	30-09-1997
		JP 3245165 B2	07-01-2002
		JP 7500321 T	12-01-1995
		KR 263494 B1	01-08-2000
		MX 9205794 A1	01-04-1993
		NO 941210 A	05-04-1994
		NZ 244660 A	26-05-1995
		PT 100938 A , B	29-10-1993
		WO 9307146 A1	15-04-1993
		US 5716954 A	10-02-1998
		ZA 9207755 A	08-04-1994